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(11) Publication number: **0 496 472 A1**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 92200160.7

(51) Int. Cl.⁵: **C08F 246/00, C08F 212/14,
G01N 33/532**

(22) Date of filing: 21.01.92

(30) Priority: 25.01.91 US 646132

(43) Date of publication of application:
29.07.92 Bulletin 92/31

(84) Designated Contracting States:
BE CH DE FR GB LI NL

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(54) **Succinimide containing polymers and latices prepared from same.**

(57) Water-insoluble, noncrosslinking, nonporous copolymers are provided which have recurring units derived from:

- (a) from 80 to 99.9 mole percent of one or more ethylenically unsaturated polymerizable oleophilic monomers which provide hydrophobicity to the copolymer, provided that none of the monomers are crosslinking monomers,
- (b) from 0.1 to 20 mole percent of one or more ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and
- (c) from 0 to 10 mole percent of one or more ionic or polar hydrophilic ethylenically unsaturated polymerizable monomers. These copolymers have a variety of uses, including diagnostic assays.

This invention relates to succinimidoxycarbonyl group-containing copolymers useful in diagnostic methods and analytical elements.

There is a continuing need in various research and industrial arts for polymerizable monomers which can be polymerized into useful copolymers.

5 Biologically active substances have been immobilized to advantage on particulate substrates such as polymeric particles. In some cases, the polymeric particulate substrates are fashioned or chemically treated to provide reactive groups on their outer surfaces for appropriate reaction with the biological substance. One means of producing such polymeric particulate substrate is to prepare the polymers with monomers having the appropriate reactive groups.

10 US-A-5,030,697 relates to a polymer-bound linkable dye having a water-soluble copolymer, a dye covalently bound thereto, and functional groups enabling the polymer dye to link covalently with biological materials.

Undesired non-specific protein adsorption has been a continual problem encountered when using polymeric material as the solid substrate in analytical and diagnostic methods. Non-specific protein 15 adsorption is of concern in affinity chromatography as well as in assays, where non-specific adsorption causes unwanted background and obscures true results.

The hydrophilic nature of the polymer surface has also been the subject of considerable research because an increase in hydrophilicity reduces adsorption of some protein but not others.

There is a need in the industry for material from which solid substrates may be made wherein the 20 material is water-insoluble, non-porous, and capable of attachment to chemical and biological materials.

The needs in the art noted above are met with a water-insoluble, noncrosslinking, nonporous copolymer,

the copolymer characterized wherein the recurring units are derived:

(a) from 80 to 99.9 mole percent of one or more ethylenically unsaturated polymerizable oleophilic 25 monomers which provide hydrophobicity to the copolymer, provided that none of the monomers are crosslinking monomers,

(b) from 0.1 to 20 mole percent of one or more ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and

(c) from 0 to 10 mole percent of one or more other noncrosslinking ethylenically unsaturated poly- 30 merizable monomers.

This invention also provides a novel aqueous latex composition comprising nonporous particles wherein at least the outer surface is composed of water-insoluble, noncrosslinked copolymer,

the composition characterized wherein the copolymer has recurring units as described above.

The advantages of the copolymers of this invention are that they contain a functional comonomer which 35 survives the polymerization process. The comonomer is capable of subsequently reacting with nucleophiles such as proteins, nucleic acids, peptides and amino acids and other amino or sulfhydryl containing materials. Also, the latex particles can be directly made without hydrolysis of the succinimidoxycarbonyl active ester group.

Further, the copolymers of the invention are hydrophobic to such a degree that they approach and are 40 more readily absorbed to the surface of the protein in comparison to the ability of known copolymers to receive protein.

The copolymers are also useful in the composition of this invention which provides particles which are colloidally stable to the biological chemistries of immobilization and detection, even when coated in a web 45 format. These particles have the additional advantages of being free of surfactants and protective colloids, nonporous, and monodisperse.

Copolymers of this invention can also be used in forming particles used to produce gel-grafted matte bead layers in photographic elements. Other photographic uses of such polymers, such as polymeric gelatin hardeners, hardenable binders or vehicles, and thickeners would also be readily apparent to a skilled 50 worker in the art.

Preferably, the polymers of this invention are used to provide reagents for medical, analytical or diagnostic methods. The structural advantages of the succinimidoxycarbonyl group in the essential monomers used herein are its reactivity with styrene monomers, its hydrophobicity and its resistance to hydrolysis.

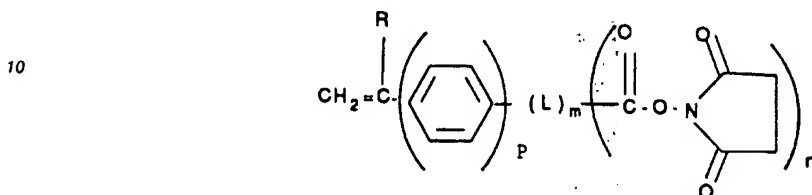
More particularly, the copolymers of this invention have recurring units derived:

(a) from 80 to 99.9 mole percent, more preferably from 90.0 to 99.9 mole percent, of one or more 55 ethylenically unsaturated polymerizable oleophilic monomers which provide hydrophobicity to the copolymer, provided that none of the monomers is crosslinkable,

(b) from 0.1 to 20 mole percent, more preferably from 0.1 to 10 mole percent of one or more

ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and (c) from 0 to 10 mole percent, and more preferably from 0 to 3 mole percent of one or more other non-crosslinking ethylenically unsaturated polymerizable monomers such as ionic or polar hydrophilic monomers.

5 Preferably, the copolymer comprises recurring units derived from monomer (b), as described above, which can be represented by the structure:



15

wherein:

R is hydrogen, alkyl of 1 to 3 carbon atoms or halo.

20 L is a linking group having at least 2 carbon atoms in the linking chain consisting essentially of a combination of at least two of alkylene groups having 1 to 8 carbon atoms, arylene groups having 6 to 12 carbon atoms, hetero atoms or heteroatom-containing groups.

m is 0 or 1, n is 1 or 2, and P is 0 or 1, with the proviso that when n is 2, one of the alkylene and arylene groups is necessarily trivalent.

25 More specifically, in the structure noted above, R is hydrogen, alkyl of 1 to 3 carbon atoms (such as methyl, ethyl, isopropyl and n-propyl), or halo (such as chloro or bromo). Preferably, R is hydrogen, methyl or chloro. More preferably, R is hydrogen or methyl.

Also, L is an organic linking group having at least 2 carbon atoms in the linking chain and is a combination of at least two of (1) alkylene groups having 1 to 8 carbon atoms, such as methylene, ethylene or trimethylene, propylene, tetramethylene, pentamethylene, or 2,2-dimethyl-1,3-propylene, (2) arylene groups having 6 to 12 carbon atoms, such as phenylene, tolylene, xylylene, naphthylene, and (3) divalent hetero atoms, such as oxygen (oxy), and sulfur (thio) atoms, or heteroatom-containing groups, such as carbonyl, sulfonyl, imino, ureylene, (-N'R where R is hydrogen or lower alkyl of 1 to 6 carbon atoms, such as methyl, ethyl, propyl, butyl, pentyl and hexyl).

35 The alkylene groups can have from 1 to 8 carbon atoms, and can be branched, linear or cyclical, substituted or unsubstituted with one or more alkyl groups (preferably from 1 to 8 carbon atoms, such as methyl, ethyl, isopropyl, hexyl and octyl), alkoxy (preferably from 1 to 12 carbon atoms, such as methoxy, ethoxy, propoxy, t-butoxy and octyloxy), cycloalkyl (preferably from 4 to 6 carbon atoms, such as cyclobutyl, cyclohexyl and cyclopentyl), aryl (preferably from 6 to 12 carbon atoms, such as phenyl, tolyl, 40 xylyl, naphthyl, 4-methoxyphenyl and chlorophenyl). Such groups are not difficult to design or synthesize for one skilled in synthetic chemistry. The arylene groups can have from 6 to 12 carbon atoms in the aromatic nucleus, and can have the same substituents as described above for the alkylene groups.

Preferably, L comprises alkyleneoxycarbonylalkylene, alkyleneethioalkyleneoxycarbonylalkylene, alkyleneiminocarbonylalkylene, iminoalkyleneoxycarbonylalkylene, alkyleneethioalkylene, alkyleneethioalkyleneiminocarbonylalkyleneoxyalkylene, alkyleneethioalkylidene, alkyleneethioalkyleneiminocarbonylalkyleneethioalkylene, alkyleneethioalkyleneiminocarbonylalkylene, alkyleneethioarylene, alkyleneethioalkyleneoxyalkyleneethioalkyleneoxycarbonylalkylene, alkyleneoxyarylenealkyleneethioalkylene, alkyleneethioalkyleneoxyalkyleneethioalkyleneoxycarbonylalkylene, alkyleneoxyarylenealkyleneethioarylenealkyleneethioalkylene, alkyleneethioalkyleneoxyalkyleneethioalkyleneoxycarbonylarylene, carbonyloxyalkyleneoxycarbonylalkylene, carbonyloxyalkyleneureylenealkylene, carbonyloxyalkyleneiminocarbonylalkylene and carbonyloxyalkyleneoxycarbonylalkylene.

Preferably, P is 1 and L is alkylenethioalkylene, ethylenethiophenylene, or alkylenethiophenylidyne.

Representative L groups include: methyleneoxycarbonyltrimethylene, methylenethioethyleneoxy-carbonyltrimethylene, methyleneiminocarbonyltrimethylene, methylene-N-methyliminoethyleneoxy-carbonyltrimethylene, methylenethioethylene, methylenethioethyleniminocarbonylmethyleneoxymethylene, methylenethio-1,1,2-ethylidinemethylenethioethyleneiminocarbonylmethylenethiomethylene, methylenethioethyleniminocarbonyltrimethylene, methylenethio-1-carboxyethylene, methylenethiophenylene, methylenethioethylenox-

yethylenethiomethyleneoxycarbonylethylene, methyleneoxyphenylenemethylenethioethylene, methylenethioethyleneoxyethylenethioethyleneoxycarbonylethylene, methyleneoxyphenylenemethylenethioethyleneoxycarbonylethylene, methylenethioethyleneoxycarbonylphenylene, and methylenethioethyleneoxycarbonylphenylene.

5 Also, m is 0 or 1, n is 1 or 2, and P is 0 or 1, with the proviso that when n is 2, one of said alkylene and arylene is necessarily trivalent.

Most preferably, P and m are both 0.

10 Preferably, monomer (b) is styrene or a styrene derivative, or an acrylic or methacrylic acid ester. More preferably, N-acryloyloxysuccinimide, 4-(2-succinimidoxycarbonylethylthiomethyl)styrene, 4-[1,2-bis(succinimidoxycarbonyl)ethylthiomethyl]styrene, or 4-(2-succinimidoxycarbonylphenylthiomethyl)styrene.

While the monomers (b) described above can be polymerized to form homopolymers, preferably they are used to prepare copolymers with one or more additional ethylenically unsaturated polymerizable monomers. For instance, the oleophilic monomers identified above as (a) are useful for providing hydrophobicity or water-insoluble properties to the resulting copolymer. A mixture of such monomers can be used if desired. Such monomers would include, but not be limited to, vinyl aromatics (for example, 15 styrene and styrene derivatives such as 4-vinyltoluene, α -methylstyrene, 2,5-dimethylstyrene, 4-t-butylstyrene and 2-chlorostyrene), acrylic and methacrylic acid esters and amides (for example, methyl acrylate, methyl methacrylate, n-butyl acrylate, 2-ethylhexyl methacrylate, benzyl acrylate and N-phenylacrylamide), butadiene, acrylonitrile, vinyl acetate, vinylbenzyl acetate, vinyl bromide, and vinylidene chloride.

20 In addition, ethylenically unsaturated polymerizable monomers (c) other than those described above for monomers (a) or (b) can be copolymerized to provide desirable properties. For example, such monomers include anionic monomers containing sulfonic acid groups or salts thereof, including 2-acrylamido-2-methylpropane sulfonic acid, 3-methacryloyloxopropane-1-sulfonic acid, p-styrene sulfonic acid and salts thereof. Also included in the (c) group of monomers are nonionic hydrophilic monomers such as acrylamide, 25 methacrylamide, N-isopropylacrylamide, 2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, pentaethylene glycol monomethacrylate, N-vinyl-2-pyrrolidone and so on. In addition, monomers having active methylene groups, such as 2-acetoacetoxyethyl methacrylate, could be used.

The method of preparing the novel copolymers described above may be accomplished using standard emulsion or suspension polymerization techniques. Pore-producing substances or inert diluents are not 30 used. If porosity is required and pore integrity needs to be maintained, the particles typically should be crosslinked so that the particles will not dissolve in the polymerization solvent or the inert diluent or pore-producing substances.

Typically, the particles of this invention are non-porous and do not require a crosslinked structure to be useful.

35 Suspension polymerization procedures are well known and generally involve mechanically dispersing the monomers in a liquid, usually water, and polymerizing the monomer droplets formed from the dispersing action. Polymerization initiators which are soluble in the monomer are generally used, and surfactants can also be used. Small particles of polymer are obtained with careful control of the polymerization conditions, which particles can be isolated using filtration, centrifugation or spray drying.

40 The copolymers of this invention are preferably prepared using emulsion polymerization techniques. In emulsion polymerization (whether batch, continuous or semi-continuous modes as known in the art), it is preferred that the copolymers be prepared as small particles without the use of surfactants (also known as emulsifiers). Further, the use of protective colloidal dispersing agents is not preferred. Residual surfactant or dispersing agents on the particles tend to interfere with attachment of biologically active substances (for 45 example, antibodies and enzymes). Thus, the resulting latex is substantially free of surfactants and colloidal dispersing agents. Conditions for surfactant-free polymerization are known in the art. Continuous polymerization is the most preferred technique so that monomers are added to a reaction vessel over a period or time.

Some general conditions for emulsion polymerization include reaction of the monomers in the presence 50 of water-soluble, free radical polymerization initiators (such as redox combinations of persulfates and bisulfites including potassium persulfate, ammonium persulfate; potassium bisulfite and sodium bisulfite and others known in the art) in an amount of from 0.1 to 5 weight % over a period of from 30 to 1200 minutes at a temperature of from 30 to 95°C. Other conditions include the use of chain transfer agents such as dodecanethiol at concentrations of from 0.05 to 5% (based on monomer weight).

55 A representative preparation of copolymers useful in this invention is provided in Example 1 below. Representative preparations of monomers useful in this invention are provided in Examples 2-4 below.

Certain preferred copolymers of this invention are generally provided in small particulate form (latices, predominantly spherical) having an average diameter of from 0.01 to 20 μ m. Preferably, the particles have

an average diameter of from 0.01 to 10 mm, and more preferably from 0.1 to 0.05 mm. The water-insoluble particles are generally nonporous and nonswellable in water or water-miscible solvents (such as alcohols), but they are also generally water-dispersible due to their small size. Polymerization procedures generally provide from 0.5 to 50 percent solids of copolymer, although, the latex composition of this invention generally has from 0.5 to 25 (preferably from 1 to 20) percent solids of copolymer particles when used.

Representative copolymers of this invention include, but are not limited to: poly[styrene-co-4-(2-succinimidoxycarbonylethylthiomethyl)styrene] (mole ratio 96.5:3.5), poly[styrene-co-4-[1,2-bis-(succinimidoxycarbonyl)ethylthiomethyl]styrene] (mole ratio 97.5:2.5).

While in most cases, the polymers of this invention are homogeneous particles, it is essential that at least the outer surface of polymeric particles be composed of a polymer of this invention. Particles having an outer shell of the polymer can be prepared by graft copolymerization or other known procedures so that an already formed particle is coated with another polymer.

All percentages in the following nonlimiting examples are by weight unless otherwise indicated.

15 EXAMPLE 1

Preparation of poly(styrene-co-N-acryloyloxy-succinimide) (96.83/3.17 molar ratio or 95/5 weight ratio).

A suitable three-neck flask (1275 mL) completely filled with distilled water was used as the reaction vessel. At 80°C, three chemical streams were simultaneously pumped into the flask. These three chemical streams comprised the following materials:

Stream 1 (monomer mix)-styrene, 765.70 g, N-acryloyloxysuccinimide, 40.73 g, dodecylmercaptan or 1-dodocanethiol, 8.06 g.

Stream 2 (oxidant)-water, distilled, 1349.91 mL, (NH₄)₂S₂O₈, 16.13 g.

25 Stream 3 (reductant)-water, distilled, 1349.91 mL, Na₂S₂O₅, 8.06 g. The pump rates were:

Stream #	Rate, g/min	Rate, mL/min
1	2.48	2.73
2	4.14	4.14
3	3.99	3.99

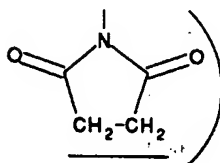
The theoretical solids based on flow are 23%, and the actual residence time was 128 minutes. After an addition time of 300 minutes, the reaction was stopped yielding 1081 grams of 21.4% solids. The resulting polymer latex was dialyzed for 5 days to yield 1366 g of purified latex of 16.2%. The NMR analysis of the polymer indicated a 97:3 mole ratio of styrene/succinimide monomers incorporated in the copolymer. Elemental analysis gave carbon of 89.78% (90.15% theory) and hydrogen 7.38% (7.50% theory). The particle size was 1.0 mm with a standard deviation of 0.05.

40 EXAMPLE 2

Preparation of 4-(2-succinimidoxycarbonylethylthiomethyl)styrene

To a stirred solution of N-hydroxysuccinimide (7.0 g, 0.06 mole), and 3-(p-vinylbenzylthio)propionic acid (13.3 g, 0.06 mole) in chloroform (100 mL) was added N,N'-dicyclohexylcarbodiimide (12.6 g, 0.06 moles) in chloroform (50 mL) at room temperature. The mixture was stirred at room temperature and the temperature of the reaction increased to 37°C. Within 5 minutes, the by-product N,N'-dicyclohexylurea began to precipitate. The reaction was stirred at 45°C in a hot water bath for 1 hour and stirring was continued at ambient temperature overnight. The precipitated N,N'-dicyclohexylurea was then removed by filtration and the solvent was evaporated in vacuo. To the residue was added diethyl ether (100 mL) and the mixture was kept at -16°C overnight. The white solid was collected by filtration, m.p. 63-68°C, yield 93%.

Analysis Calculated for C₁₆H₁₇NO₄S: C, 60.17, H, 5.37, N, 4.39, S, 10.04. FOUND: C, 59.32, H, 5.35, N, 4.77, S, 9.23. ¹H NMR (CDCl₃) δ 2.8 (broad singlet, 8H, CH₂CH₂).



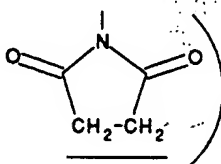
3.7 (s, 2H, ArCH_2 S), 5.15 and 5.7 (AB quartet, 2H, CH_2 =), 6.7 (m, 1H, CH =), 7.3 (m, 4H, Ar H's).

10 EXAMPLE 3

Preparation of 4-[1.2-Bis(succinimidoxycarbonyl)ethyl-thiomethyl]styrene

This compound was prepared by the same procedure described above to give a white solid, which was recrystallized from dichloromethane/ethylacetate (4:1), m.p. 118-120 °C with polymerization, yield 83%.

Analysis Calculated for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_8\text{S}$: C, 54.78, H, 4.38, N, 6.08, S, 6.96. FOUND: C, 54.63, H, 4.41, N, 6.11, S, 7.36, ^1H NMR (CDCl_3) δ 2.8 + 2.85 (2 singlets, 8H,



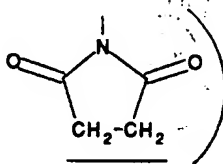
3.2 (m, 2H, $\text{CH}_2\text{-CO}_2\text{NHS}$), 3.95 (t, 1H, S- CH-C), 4.05 (s, 2H, $\text{CH}_2\text{-S}$), 5.2 and 5.75 (AB quartet, 2H, CH_2 =), 6.7 (m, 1H, CH =), 7.38 (m, 4H, ArH's).

30 EXAMPLE 4

Preparation of 4-(2-succinimidoxycarbonylphenylthio-methyl)styrene

This compound was prepared by the same procedure described above to give a white solid which was crystallized from dichloromethane (100 ml)/ethyl acetate (80 ml), m.p. 155-7 °C, yield 80%.

Analysis Calculated for $\text{C}_{20}\text{H}_{17}\text{NO}_4\text{S}$: C, 65.38, H, 4.66, N, 3.81, S, 8.73. FOUND: C, 64.91, H, 4.97, N, 3.97, S, 7.87, ^1H NMR (CDCl_3) δ 2.8 (s, 4H,



4.2 (s, 2H, $\text{CH}_2\text{-S}$), 5.2 and 5.7 (AB quartet, 2H, CH_2 =), 6.65 (m, 1H, CH =), 7.0-8.2 (m, 8H, ArH's).

Claims

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1. A water-insoluble, noncrosslinked, nonporous copolymer,

the copolymer characterized wherein the recurring units are derived:

55

(a) from 80 to 99.9 mole percent of one or more ethylenically unsaturated polymerizable oleophilic monomers which provide hydrophobicity to the copolymer, provided that none of the monomers are crosslinking monomers,

(b) from 0.1 to 20 mole percent of one or more ethylenically unsaturated polymerizable monomers having a succinimidoxycarbonyl group, and

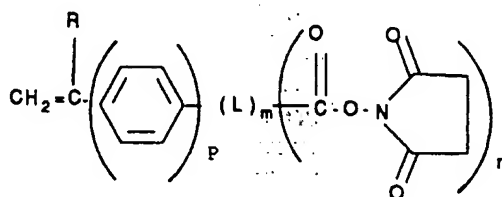
(c) from 0 to 10 mole percent of one or more other ethylenically unsaturated polymerizable

monomers.

2. The copolymer as claimed in claim 1 having from 0 to 3 mole percent of recurring units derived from monomer (c).

3. The copolymer as claimed in either of claims 1 or 2 having from 0.1 to 10 mole percent of recurring units derived from (b).

4. The copolymer as claimed in any of claims 1 through 3 wherein monomer (b) is represented by the structure:



wherein:

R is hydrogen, alkyl of 1 to 3 carbon atoms or halo,

L is a linking group having at least 2 carbon atoms in the linking chain and is a combination of at least two of (1) alkylene groups having 1 to 8 carbon atoms, (2) arylene groups having 6 to 12 carbon atoms, and (3) hetero atoms or heteroatom-containing groups,

m is 0 or 1, n is 1 or 2, and P is 0 or 1,

with the proviso that when n is 2, one of said alkylene and arylene is necessarily trivalent.

5. The copolymer as claimed in claim 4 wherein R is hydrogen, methyl, or chloro.
6. The copolymer as claimed in claim 4 wherein monomer (b) is N-acryloyloxy-succinimide, 4-(2-succinimidoxycarbonylethyl-thiomethyl)styrene, 4-[1,2-bis(succinimidoxycarbonyl)ethylthiomethyl]styrene, or 4-(2-succinimidoxycarbonylphenylthiomethyl)styrene.

7. An aqueous latex composition comprising nonporous particles wherein at least the outer surface is composed of a water-insoluble, noncrosslinked copolymer, the composition characterized wherein the copolymer is that claimed in any of claims 1 through 6.

8. The composition as claimed in claim 7 wherein the composition is substantially free of surfactants and protective colloidal dispersing agents.

9. The composition as claimed in either of claims 7 or 8 wherein the particles have an average diameter of from 0.01 to 10 mm.

10. The composition as claimed in any of claims 7 through 9 wherein the composition has from 0.5 to 25 percent solids of the copolymer particles.



European Patent
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EUROPEAN SEARCH REPORT

Application Number

EP 92 20 0160

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 331 633 (CIBA-GEIGY AG) ---		C08F246/00 C08F212/14 G01N33/532
A	CH-A-601 364 (CIBA-GEIGY AG) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C08F
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 13 MAY 1992	Examiner CAUWENBERG C. L.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document	